CURRENT CONCEPTS

Molecular Biology of Flexor Tendon Healing in Relation to Reduction of Tendon Adhesions

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Tendon injuries are encountered after major and minor hand trauma. Despite meticulous repair technique, adhesion formation can occur, limiting recovery. Although a great deal of progress has been made toward understanding the mechanism of tendon healing and adhesions, clinically applicable solutions to prevent adhesions remain elusive. The goal of this paper is to review the most recent literature relating to the tendon healing and adhesion prevention. *(J Hand Surg Am. 2017;■(■):■−■. Copyright © 2017 by the American Society for Surgery of the Hand. All rights reserved.)*

Key words Tendons, flexor, adhesions, prevention.

In the United States, nearly 1.5 million emergency room visits per year are due to flexor tendon injuries.[1] Up to 30% to 40% of these injuries end up with postsurgical adhesion formation between the tendon and the surrounding tissues; these form as a result of disruption of the gliding mechanism due to puncture, laceration, or compression of the tendon.[2] For the patient, this translates to poor digital range of motion (ROM).

Tendon healing occurs through 2 simultaneous pathways. Intrinsic healing involves proliferation of tenocytes and production of extracellular matrix (ECM); extrinsic healing involves invasion of cells from the surrounding sheath and synovium, which envelop the tendon structure, contributing to adhesion formation.[3] Tendons inherently have minimal capacity for intrinsic healing owing to poor cell density and growth factor activity. Extrinsic healing dominates when the tendon or tendon sheath is injured.

Strategies for adhesion prevention manipulate either mechanical or biological factors. Mechanical factors targeted include early postoperative mobilization and atraumatic handling of tendons, whereas biological-themed approaches include the use of chemical and molecular modulation of scar formation.[4] Recent basic science research has focused on the molecular events in the tendon healing process, tendon tissue engineering, and biological approaches that enhance healing. This article reviews the available scientific evidence behind both current and potential approaches to preventing adhesion formation following flexor tendon repair.

TENDON HEALING PROCESS

Flexor tendons heal via intrinsic and extrinsic pathways in sequential and partially overlapping phases: inflammation, proliferation, synthesis, and remodeling, including apoptosis/necrosis and vascularization.[5] Following injury, an acute inflammatory response is initiated, resulting in recruitment of circulating inflammatory cells including macrophages, monocytes, and neutrophils. This phase lasts approximately 3 to 7 days. Extrinsic cells, from the peritendinous soft tissue, as well as intrinsic cells, from the epitenon and endotenon, migrate and proliferate in the area of the

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tendon injury. They form the granulation tissue present in the proliferative stage. In the subsequent fibroblastic proliferative phase, extracellular membrane components, including collagen type III, are deposited, initially randomly. In the later remodeling phase, they are reorganized into longitudinal structures. Around the fourth week, fibroblasts intrinsic to the endotendon begin to proliferate and play an important role in resorption of collagen and production of new collagen. Over the span of the ensuing 2 months, the tendon tissue matures and the fibers are oriented longitudinally owing to the prevailing tension forces. Part of the tendon maturation process involves conversion to type I collagen and cross-linking between collagen structural units that ultimately provides strength for the healed tendon.[6]

IMPACT OF MECHANICAL LOAD ON TENDONS

Tenocytes respond to mechanical stress cues by modifying the expression of ECM components and matrix degradation enzymes with the goal of guiding tendon maturation toward structural healing. Through mechanical stress input, tenocytes upregulate the expression of type III collagen mRNA expression and increase the concentration of growth factors, resulting in cell proliferation, differentiation, and matrix formation.[7] Thus, tendon healing is increased along the intrinsic pathway and adhesions are decreased. In contrast, risk of rupture increases if there is a lack or overstimulation of the tendon repair due to accumulation of lipids, mucoid formation, and tissue calcification.

CYTOKINES AND BIOLOGICAL MEDIATORS

A great deal of research has been devoted to understanding the biomechanical pathway to tendon adhesion formation. Unfortunately, this has led to little progress in effective clinical application. However, these studies have identified critical growth factors, resulting in targeted studies to uncover treatment modalities that may be clinically applicable in the future.

Transforming growth factor-beta

The transforming growth factor-beta (TGF-β) has 3 main isoforms (β1, β2, β3) and is found throughout the body. Whereas small amounts are present within the uninjured native tendon and surrounding sheath, tendon injury stimulates increased production of TGF-β. As a result, the inflammatory response is amplified through maturation of monocytes into macrophages. All 3 isoforms are involved in the production of collagen type I and type III, fibronectin, and glycosaminoglycans. Of the 3 isoforms, TGF-β1 has the highest association with adhesion formation and is thus a major target for treatment. Blocking TGF-β1 has resulted in improved ROM and decreased collagen production.[8] A recent animal study by Maeda et al[9] demonstrated that, after acute tendon transection, disruption and destabilization of the ECM occur, leading to excessive release of TGF-β1. The elevated levels manifest as massive tenocyte death. The TGF-β1 receptor inhibitor SD208 can prevent progression of this pathway and improve tendon mechanical strength, decreasing rupture rates.

However, there is contradicting evidence that blocking TGF-β1 or SMAD 3 pathway can actually result in reduced tendon strength.[10] Most recently, Wu et al[11] used an adeno-associated virus vector to transfer TGF-β1 microRNA into chicken digital flexor tendons and observed a dose-related improved tendon gliding and decreased adhesion formation versus controls. At the same time, the decreased TGF-β1 concentration resulted in weakening of tendon versus controls. Methods to primarily isolate the beneficial effects of TGF-β1 remain elusive and more research is necessary to uncover clinical applications.

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) shares 20% amino acid homology with platelet-derived growth factor. The VEGF family consists of several isoforms (VEGF-A, -B, -C, -D and -E and placenta growth factor) as a result of alternate splicing of its mRNA. The VEGF isoforms exert their biological activity through 3 tyrosine kinase receptors, but the bioavailability depends on the isoform binding to the receptor. The VEGF has been associated with dermal wound healing through epithelization, collagen deposition, and angiogenesis.[12] However, VEGF-A (VEGF165) has been also been associated with dermal scarring, which suggests that supplementing VEGF-A to increase angiogenesis may have an undesired effect on scarring.[13]

In vitro assays have suggested that, when compared with other exogenous genes, plasmids containing the VEGF cDNA have little or no effect on flexor tendon–derived fibroblasts in either cell proliferation or collagen synthesis.[14] However, a further study showed that, during flexor tendon repair, VEGF mRNA is increased, peaking at days 7 to 10, but returning to baseline by day 14, which suggests a time-dependent function.[15] Researchers theorize this could be neovascularization around the repair site because studies have suggested an increase in blood vessel density, peaking at day 17.[16] In an Achilles tendon model,